HARRIS PASTIDES, PH.D.
37 WILDFLOWER DRIVE, AMHERST, MASSACHUSETTS 01002 (413) 256-0778

October 28, 1997

NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee
c/o Dr. Larry G. Hart, Executive Secretary
NIEHS
Research Triangle Park, NC
VIA FACSIMILE: 919 541-0295

Re: RC Draft Background Document for TCDD

Dear Members of the Subcommittee:

Please find enclosed a copy of my comments on the RC Draft Background Document for TCDD. I prepared these in response to a request by the American Forest and Paper Association to provide an independent assessment of this document.

I hope that these comments will be of value to you. Please do not hesitate to be in touch with me should you wish to have clarification or further information on any of my observations.

Sincerely,

H Pastides

Harris Pastides, Ph.D.

Enclosures

Comments on RC Draft Background Document for TCDD

Harris Pastides, Ph.D.
Amherst, Massachusetts

This document would classify 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD or dioxin) as "known to be a human carcinogen." In its rationale for this classification the document reports that human studies have found an association between dioxin exposure and cancer mortality from all sites combined, from non-Hodgkin's lymphoma, and from lung cancer. This assertion appears to represent the central reasoning for assigning this categorization since the other lines of supporting evidence relate to studies of experimental animals and theories about dioxin's mechanism of tumor induction. Therefore, the assertion relating to human evidence, and the evidence supporting this claim, need to be evaluated critically.

<u>Assertions of the RC Document</u>

1. The document states that epidemiological studies of high exposure occupational cohorts have reported a statistically significant increase in relative risk for all cancers combined, lung cancer, and non-Hodgkin's lymphoma. The document also states that the 1997 IARC Working Group "noted" a causal relationship between TCDD exposure and all cancers combined.

These statements are not factual conclusions or interpretations of the IARC report and oversimplify the Working Group's conclusions. IARC's actual commentary, as reported in Section 5.2 (pp. 336-7) of the Monograph, is as follows:

• The magnitude of the increase for all cancers combined is "generally low" and is higher in sub-cohorts with heaviest exposure.

• A statistically significant positive dose-response trend between all cancers combined and increasing exposure was seen in one cohort and a non-significant trend was seen in another but only among smokers.

• The increased relative risk for lung cancer in the combined highly exposed sub-cohorts was statistically significant but the standardized mortality ratio point estimate was only 1.4. IARC concluded that a variety of other possible risk factors including occupational carcinogens, could be contributing bias due to confounding.

• The increased risk for non-Hodgkin's lymphoma was weak and inconsistently observed; caution against a causal interpretation is made explicitly.

• The strongest evidence is for all cancers combined. This statement is made, however, relative to the inconclusive evidence for the site-specific results noted above. Furthermore, IARC noted that confounding could not be ruled out as an explanation for the relative risk of 1.4 observed in the most heavily exposed and longest latency sub-cohorts. The IARC committee also acknowledges the lack of precedence for a multi-site carcinogen without concomitant findings of a dominant specific site and, in this light, recommends a cautious interpretation of the observed data on total cancer risk.

The IARC conclusion is that the epidemiological data are limited and are insufficient for determining that TCDD is a human carcinogen. Therefore, the RC document's assertion on page 3-2 that "...the IARC Working Group identified a causal association between TCDD exposure and all cancers combined... " is not an accurate representation of IARC's summary and conclusion. Also, it is not a sensible epidemiological statement in that causal associations are <u>never</u> determined solely on the basis of one or more epidemiological studies; they are determined by evaluating numerous criteria some of which are not directly addressed in observational studies (i.e. Hill postulates).

The RC document misinterprets IARC's comment that the evidence of increased risk for all cancers combined is "strongest" as a conclusion that the evidence for TCDD's carcinogenicity in humans is sufficient. In fact, the IARC statement about the strength of the evidence is offered relative to the site-specific findings only.

2. The RC document suggests that the additional findings contained in the recently published follow-up study from Seveso by Bertazzi et al. (Epidemiology 1997; 8:646-652.) "strengthen the associations reviewed by IARC in an important way." The implication is that these results may "tilt the scale" in favor of a conclusion regarding human carcinogenicity. In truth the new paper, while providing some new insights about TCDD cancer risk by latency and duration of exposure, does not substantively clarify the complex relationship between TCDD and human cancer. Specific results of the extended follow-up paper include:

• No meaningful increase in all cancer mortality for males or females in any exposure zone (low, medium, high) between 1976-1991 (Tables 3 and 4).

• No evidence for an increasing trend of all cancer mortality and latency or length of residence in the contaminated area among males in Zone B (Table 5). The trends that were observed comprised sites for which TCDD has not been strongly linked to in the larger body of literature (rectal cancer and esophageal cancer, primarily).

• Among females in Zone B a modest trend with all cancer mortality and latency and duration was observed but the strongest trends were for stomach and other digestive tract cancers. The trend with lymphatic and hematopoietic cancer was also present but not as strong.

Most of these trends are not confirmed by other cohort studies which had the opportunity to examine latency and duration of occupational exposure; these results are summarized in the IARC Monograph.